TITLE: **CHRONIC CONSTIPATION IN ADULTS: CONTEMPORARY PERSPECTIVES AND CLINICAL CHALLENGES. 1: EPIDEMIOLOGY, DIAGNOSIS, CLINICAL ASSOCIATIONS, PATHOPHYSIOLOGY AND INVESTIGATION**

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ABBREVIATIONS:

ACE	antegrade continence enema
BET	balloon expulsion test
CC	chronic constipation
ED	evacuation disorders
FC	functional constipation
FDD	functional defaecation disorders
GI	gastrointestinal
GP	general practitioners
HR-ARM	high-resolution anorectal manometry
IBS-C	irritable bowel syndrome with constipation
MRI	magnetic resonance imaging
OIC	opioid-induced constipation
PRO	patient-reported outcomes
RH	rectal hyposensitivity
ROM	radio-opaque markers
SCFA	short-chain fatty acids
STC	slow-transit constipation
WMC	wireless motility capsule

ABSTRACT

BACKGROUND

Chronic constipation is a prevalent disorder that affects patients' quality of life and consumes resources in healthcare systems worldwide. In clinical practice, it is still considered a challenge as clinicians frequently are unsure as to which treatments to use and when. Over a decade ago, a *Neurogastroenterology & Motility* journal supplement devoted to the investigation and management of constipation was published (2009;21(Suppl.2)). This included seven articles, disseminating all themes covered during a preceding two-day meeting held in London, entitled 'Current perspectives in chronic constipation: a scientific and clinical symposium'. In October 2018, the 3rd London Masterclass, entitled 'Contemporary management of constipation' was held, again over two days. All faculty

members were invited to author two new review articles representing a collective synthesis of talks presented and discussions held during this meeting.

PURPOSE

This article represents the first of these reviews, addressing epidemiology, diagnosis, clinical associations, pathophysiology and investigation. Clearly not all aspects of the condition can be covered in adequate detail; hence, there is a focus on particular 'hot topics' and themes that are of contemporary interest. The second review addresses management of chronic constipation, covering behavioural, conservative, medical and surgical therapies.

AUTHORS' CONTRIBUTIONS:

SMS conceived the idea of these review articles. All authors performed the literature search and wrote the manuscript according to the section they were assigned: Introduction: SMS, MC, CK; Epidemiology and diagnosis: MS, JR-T, ED, AF. Clinical associations: ADF, SMS, AF, KN. Pathophysiology: PD, SMS, RB, CK, KW. Investigation: EC, MF, RB, PD, CH, KK. Section Leads were: SMS, MS, ADF, PD and EC. Initially, SMS collated and revised all sections of the manuscript. Section Leads and finally all authors critically revised subsequent versions of the manuscript and approved the final version.

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CK is a paid Consultant and speaker for Medtronic Inc. He has consulted in the last 3 years for Coloplast, Enetromed and Alimentary Health. He has received funding for research activities from Saluda Medical, Cook Medical, Exero Medical and Takeda. He is a member of committees that benefit from industry sponsorship including the Rome Foundation and The International Anorectal Physiology Working Group.

KN has consulted in the last year for Coloplast.

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INTRODUCTION

Chronic constipation (CC) remains a clinical challenge, with frequent suboptimal outcomes to a variety of conservative, behavioural, medical and surgical interventions. Over a decade ago, a *Neurogastroenterology and Motility* journal supplement was devoted to the investigation and management of constipation (2009:21 [Suppl. 2]). This included seven articles,[1-7] disseminating all themes covered during a preceding two-day meeting held in London, entitled 'Current perspectives in chronic constipation: a scientific and clinical symposium'. In October 2018, the 3rd London Masterclass, entitled 'Contemporary management of constipation' was held, again over two days, and again boasting a world-renowned faculty. By way of dissemination, two side-by-side review articles have been produced that represent a collective synthesis of talks presented and discussions held during this meeting. Authorship includes all invited faculty members. These reviews provide not only an update on topics addressed in the previous journal supplement, but also a state-of-the-art overview of the clinical management of constipation. Areas for future research are additionally highlighted. The first of these reviews addresses epidemiology, diagnosis, clinical associations, pathophysiology and investigation. Clearly not all aspects of the condition can be covered in adequate detail; hence, there is a focus on particular 'hot topics' and themes that are of contemporary interest. The second, 'sister' review, addresses management of chronic constipation, encompassing behavioural, conservative, medical and surgical therapies.

EPIDEMIOLOGY AND DIAGNOSIS

Definitions

Constipation is most simplistically defined as unsatisfactory defaecation resulting from infrequent stools, difficult stool passage, or both.[8] Alternatively, it is a term that embraces a (limited) spectrum of symptoms related to an individuals' personal dissatisfaction with their evacuatory ability.[4] Symptoms include, though are not restricted to, hard stools, excessive straining, infrequent bowel movements, bloating and abdominal pain,[9] and if such symptoms last >1 month, constipation is labeled as chronic. CC can be viewed as an umbrella term encompassing all disorders and conditions with long-standing constipation, and can be primary or secondary. Multiple conditions may cause secondary CC, for example, drugs (opioids, calcium channel blockers, NSAIDs), neurological disorders (Parkinson's disease), or metabolic diseases (diabetes).[10] Primary CC (which is the main focus of these reviews) is a condition that is considered to result from dysfunction of colonic regulation of stool

movement, together with uncoordinated or obstructed defaecation, with or without simultaneous abnormal gastrointestinal (GI) sensitivity (hyper- or hyposensitivity).[11,12]

Epidemiology

When reviewing the epidemiology of CC, it is important to acknowledge that definitions vary across studies (see below). Nevertheless, CC is extremely common amongst adults in the community, with the most recent systematic review and meta-analysis (incorporating 45 population-based studies) showing a global prevalence of 14%.[10] Prevalence increases with age,[10,13-15] and is almost twice as common in women than men.[10] The meta-analysis also showed a modest increase in prevalence of CC among individuals with the lowest socioeconomic status compared to those with the highest (OR 1.32; 95% CI: 1.11 – 1.57),[10] supporting the results of other previous studies.[15,16]

Impact of CC on quality of life appears comparable with that of some organic conditions, including chronic obstructive pulmonary disease, diabetes, and depression,[17] and up to 20% of people with CC will ultimately consult a physician.[18] In a recent report on the cost of constipation in the UK, it was estimated that 2 million people suffer from CC, yet up to one-in-five are reluctant to talk to their doctor about their symptoms.[19] The same report also suggested that between 2017 and 2018, almost 200 people were admitted to hospital each day as a result of CC, equating to >160,000 bed days per year, and treatment costs in excess of £160 million, including >£70 million for unplanned admissions and >£90 million for laxatives.[19]

Diagnosis and symptom assessment

Constipation is generally considered a symptom-based disorder, with subtypes able to be defined according to the use of diagnostic criteria, such as the Rome IV criteria,[20] which are advocated together with a limited number of tests to rule out other diagnoses, as well as for ensuring eligibility for clinical trials.[21] The Rome IV criteria allows categorisation of disorders of CC into four subtypes: (a) functional constipation (FC), (b) irritable bowel syndrome with constipation (IBS-C), (c) opioid-induced constipation (OIC), and (d) functional defaecation disorders (FDD), the latter including inadequate defaecatory propulsion and dyssynergic defaecation.[20-22] IBS-C is characterized by a combination of pain and constipation; FC by the presence of constipation symptoms without predominant pain and/or bloating (i.e. criteria for IBS is not met); OIC as new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy; and FDD as symptoms compatible with IBS-C or FC in combination with objective signs of disturbed rectal evacuation on diagnostic testing. [20-22]

Conversely, based on presence or absence of detectable physiological abnormalities on diagnostic testing, at least three subtypes of CC (which may overlap) have been described: slow-transit constipation (STC), evacuation disorders (ED, which encompasses structural or functional obstructive phenomena that impede stool expulsion), and normal transit constipation. More widespread use of physiological tests to better define clinical / physiological phenotypes could, in the future, pave the way for improved management of constipation. For example, establishing a diagnosis of a FDD implies the need to use a specific treatment such as biofeedback therapy.

Other available diagnostic tools include the Bristol Stool Form scale, which is a 7-point scale (ranging from separate hard lumps to liquid consistency with no solid pieces) used extensively in clinical practice and research for stool form measurement.[23] This non-expensive and widely available instrument has been shown to be a reliable surrogate marker for whole-gut and colonic transit,[24] and has been adapted into several languages and been modified for use in children.

In CC, as in many other chronic diseases where objective findings correlate poorly with reported symptoms, patient-reported outcomes (PRO) are of great importance to evaluate the effectiveness of treatments and disease progression over time. Tools that currently exist to evaluate PRO measures, developed through literature review and input from patient focus groups, include the Patient-Reported Outcomes Measurement Information System (PROMIS) GI symptom item bank,[25] which captures symptoms in 8 domains, including constipation,[26] and the CC Symptom Severity Measures.[27] The Measure Yourself Medical Outcome Profile (MYMOP), a patient-generated outcome measure allowing patients to select the problems that are the most important to them, has also been used in patients with CC.[28] Additionally, several specific constipation questionnaires have been developed such as the Patient Assessment of Constipation Symptoms (PAC-SYM), a 12-item self-report instrument divided into abdominal, rectal and stool domains.[29] PAC-SYM has been used in several clinical trials and is considered a reliable and valid tool in adult patients. Other validated scores, such as the Cleveland Clinic constipation score (CCCS)[30] and the Knowles-Eccersley-Scott-Symptom (KESS) score[31] have been developed to identify subtypes of CC more from a clinical than a mechanistic perspective.

Perceptions of constipation

Despite the existence of formal diagnostic criteria for constipation disorders (e.g. Rome criteria),[20,32] evidence suggests that patients and clinicians often diagnose CC more pragmatically, based on the assessment of symptoms *they* consider important for a diagnosis. Indeed, a study showed that general

practitioners (GPs) did not typically use the Rome criteria in clinical practice, and focused only on stool frequency and consistency to diagnose CC.[33] Similarly, a recent cross-sectional study in 2,557 members of the general population, 411 general practitioners and 365 specialist gastroenterology doctors demonstrated that only 46%-58% of the general population and 39%-73% of clinicians correctly identified FC when provided with case studies of patients meeting the Rome IV criteria for functional constipation.[34] The same study also highlighted differences in symptoms perceived to be important for a diagnosis of constipation; for example, infrequent bowel movements was most frequently reported as important for a diagnosis by specialist gastroenterologists and colorectal surgeons, compared to less than a third of constipated and non-constipated members of the general population.[34] Moreover, this and other studies indicate that symptoms outside of the Rome criteria, such as pain during defaecation and spending a long time on the toilet without passing a stool, are used by the general population to define CC, confirming differences in perceptions of CC between the general population and clinicians.[34-36] Such differences may impact patients' clinical care, including diagnosis and treatment, reinforcing the need to also use PRO measures in clinical practice to assess patients' individual needs.

Disorders with chronic constipation: are they distinct entities?

Accumulating clinical and mechanistic evidence suggests that the different disorders of CC exist on a spectrum rather than being distinct entities, as highlighted in the most recent version of the Rome diagnostic criteria for functional bowel disorders.[20,37] It is further acknowledged that it is sometimes difficult to distinguish one from another, as overlap commonly exists, and that transition from one functional bowel disorder or from one predominant symptom to another is frequently seen. Specifically, considerable overlap between IBS-C and FC exists when mutual exclusivity is suspended, [38-41] and transition from FC and IBS-C, and *vice versa*, is common.[41,42] Also, when reviewing studies assessing the pathophysiology of IBS-C and FC, a considerable overlap can be seen, even though certain abnormalities, e.g. visceral hypersensitivity seems to be more prominent in IBS, and others, e.g. abnormal colonic motility, seem to be more related to FC (Figure 1).[43]

Paediatric chronic constipation and transition to adult medical care

There are similarities between paediatric and adult constipation (e.g. hard stools, with painful and infrequent bowel movements, often accompanied by symptoms of bloating and abdominal pain).[44] However, in contrast to adults, children more often present with coexistent faecal incontinence, caused by overflow of soft stools passing around a rectal faecal mass. Moreover, children rarely complain of the sense of incomplete evacuation or obstruction, or the requirement of manual

manoeuvres to defaecate. Further, differences in response to conventional strategies such as biofeedback therapy and pharmacotherapy, and different surgical outcomes following neuromodulation and antegrade continence enema (ACE) surgery, suggest that childhood functional constipation may be a different entity from adult functional constipation.[44] However, transition to adult care is of fundamental clinical importance, since a long-term follow-up study (median follow- up of 11 years) showed that 25% of children still experience symptoms of constipation as adults, and that many continue to have severe symptoms.[45] A recent UK guideline on transition of adolescent and young persons with chronic GI conditions from paediatric to adult care recommends the use of structured transition programmes to improve GI disease control, which better ensures adherence to medications, clinic attendance and clinical outcomes.[46] In addition, such programmes may improve psychological outcome and health-related quality of life, and may reduce adverse outcomes such as hospitalisation and surgery. Currently, however, outpatient transition clinics exist for patients with inflammatory bowel disease, but are lacking for patients with functional gastrointestinal disorders, including constipation.[47]

Areas for future research

1. More information about the costs of constipation to health services, and society as a whole, globally.
2. Further exploration of means to facilitate the transition from adolescents with CC to presentation in adult gastroenterology care.
3. Better understanding of risk factors for constipation in the community.
4. Defining relevance of results from (patho)physiological testing for symptoms and outcome of treatment in patients suffering from constipation with and without other accompanying GI symptoms.
5. Can more detailed assessment of the symptom profile (standardised questionnaires, bowel habit diaries etc.) predict physiological abnormalities among patients with constipation symptoms?
6. Are there specific and clinically relevant phenotypic subgroups among subjects presenting with constipation, and can these subgroups can be reliably (and cost-effectively) identified in the clinical setting.
7. Integration of doctors' and patients' perceptions of a constipation diagnosis into the formal diagnostic criteria for constipation; this will also be informed by a better understanding of PRO measures.

CLINICAL ASSOCIATIONS

A number of clinical conditions are associated with CC, and a comprehensive review of all is beyond the scope of this review. Nevertheless, several conditions are of notable contemporary interest, as the knowledge base regarding their association with CC accumulates. These include: (1) faecal incontinence (FI), whose coexistence with CC has been grossly underappreciated in adult populations; (2), connective tissue disorders, especially hypermobile Ehlers-Danlos syndrome (hEDS); (3) post-surgical intervention, most notably following surgery for colorectal cancer; (4) as a sequelae to opioid therapy, given the current opioid epidemic in Western society, and (5) comorbid mood disorders.

Faecal incontinence

FI affects 8 – 12% of the adult population[48-50] and can have a devastating negative impact on quality of life.[51] Though long-considered to predominantly affect females secondary to obstetric-related anorectal injury, recent epidemiological studies show prevalence is equivalent between genders,[48,49] indicating that pathoaetiological factors other than traumatic childbirth *must* play a role.[52,53] Loose stools and faecal urgency are key, well recognised risk factors for FI,[48,54,55] but in both paediatric[56,57] and geriatric populations,[58,59] a major underlying cause for FI (in >80% of patients) is considered to be constipation.[60] Unfortunately, this relationship has been grossly neglected in the general adult population. However, recent data indicate that in a sizeable proportion of patients (up to 69%), significant symptoms of FI and CC coexist;[61-65] with recognition of this frequently overlooked by the referring clinician.[65]

Pathophysiology of concurrent FI and constipation is undoubtedly multifactorial, though coexistence suggests some commonality of underlying mechanisms (see Figure 2).[60,66] Over 30 years ago, Swash *et al.* proposed a unifying hypothesis for pelvic floor disorders (including constipation) and FI which still holds merit today, where obstetric injury (females) or constipation (males and females), characterised by chronic straining at stool, lead to denervation of the pelvic floor and anal sphincter musculature and ultimately to FI, with consequent pelvic floor descent (and possibly prolapse) resulting in progression of the neurogenic lesion.[67] They have recently revised this hypothesis to include traction injury to pelvic floor suspensory ligaments, with laxity leading to inactivation of anorectal muscle force vectors during defaecation and worsening of the (underlying) evacuation disorder.[68] Other important pathophysiological mechanisms include 'overflow' secondary to faecal impaction (e.g. with a megarectum or severe evacuation disorder, often allied to hyposensitivity),[69,70] or where FI results

from incomplete rectal evacuation whether by structural[65,71,72] or functional cause,[73] often in the presence of abnormal anal sphincter function / structure.[65]

Acknowledgment of coexistent FI and constipation has major implications regarding management. If FI is indeed secondary to underlying constipation, then intervention directed to improving constipation symptoms and efficacy of evacuation should be considered first-line treatments. Several studies have demonstrated significant improvements or resolution of symptoms of FI when causes of evacuatory dysfunction have been addressed (e.g. after surgical repair of rectocoele and / or intussusception,[74-76] and following colorectal irrigation).[77]

Connective tissue disorders

Constipation is present in up to 50% of patients with connective tissue disorders, be they inflammatory (e.g. systemic sclerosis: SSc) or non-inflammatory (e.g. hEDS),[78,79] and this is more common in patients who have systemic involvement.[78,80] GI symptoms can precede the systemic manifestations and therefore the diagnosis of a connective tissue disorder.

SSc is characterized by autoimmune-mediated neuropathy, myopathy and fibrosis within the GI tract. Constipation is most common in those patients with upper GI involvement, and can be due to slow gastrointestinal transit[81] or anorectal dysfunction.[82] In severe cases, gut dysmotility caused by the underlying pathology can lead to chronic intestinal pseudo-obstruction. Prucalopride, stimulant laxatives and, in refractory cases, neostigmine can be effective for slow-transit constipation in SSc.[83] Fibre worsens bloating and should be avoided.[84] In terms of anorectal dysfunction, anal hypotension, a reduced or undetectable recto-anal inhibitory reflex[85] and increased rectal sensitivity to balloon distension[86] are typically seen on diagnostic testing. Over time, symptoms of diarrhoea and FI can develop due to the development of small intestinal bacterial overgrowth and atrophy of the internal anal sphincter, respectively, both consequences of the underlying connective tissue disorder.[87]

Ehlers Danlos Syndrome (EDS) is a non-inflammatory connective tissue disorder characterised by joint hypermobility, tissue fragility and musculoskeletal symptoms. hEDS is the most common subtype of EDS and is the only one in which the aetiology and genetic marker have not been identified. The prevalence of constipation is higher in hEDS than in other EDS subtypes.[88] Constipation can be present from early life,[89] with progression to an alternating bowel habit in some.[90] Symptoms of an ED are very common,[91] and there is a high prevalence of rectal hyposensitivity,[89] dyssynergic defaecation and rectal morphological abnormalities.[62] Colonic transit may be delayed,[88] though this may be secondary

to a coexistent ED. Treatment is holistic, involving lifestyle advice, opiate withdrawal, and laxatives/irrigation therapy as appropriate for the underlying pathophysiology. Surgery for constipation in SSc and hEDS is relatively contraindicated because of the risk of anaesthetic complications, wound problems and postoperative ileus.[92,93]

Following colorectal surgery

Colorectal cancer is the third most common cancer, with 1.8 million new cases diagnosed worldwide in 2018;[94] the majority of these will be treated surgically, and 50-60% of patients now survive long-term (greater than 10 years). New symptoms of bowel dysfunction are common post-operatively. For example, symptoms such as FI, faecal urgency, constipation, fragmentation of stool, and frequent bowel movements constitute a major problem following low anterior resection (LAR),[95] which is performed in up to 80% of patients undergoing surgery for rectal cancer.[96] These symptoms are collectively referred to as the low anterior resection syndrome (LARS), with 40-50% of patients having long-term LARS to an extent that it significantly impairs their quality of life.[97,98] In patients undergoing surgery for colon cancer, a recent study showed that 21% suffered from LARS-like symptoms post-opertaively;[99] this is a similar proportion to the number of patients reporting a sense of incomplete rectal emptying after sigmoid colectomy.[100]

The reasons behind the poor functional results after both rectal and colon cancer surgery have yet to be established, though tumour height and location, gender and preoperative radiotherapy are important factors. Pathophysiology is considered to be multifactorial,[96] with loss of neurological continuity, compromised neorectal sensory-motor function allied to surgical excision of the rectal reservoir,[96,101] anal sphincter dysfunction[102,103] and increased colonic motility[104,105] considered primary mechanisms. Management following bowel cancer surgery is empirical and symptom-based, using existing therapies for FI, urgency, evacuatory difficulties etc.[96]

Opioid-induced constipation

Opioids are associated with substantial adverse effects, including those arising from the GI tract such as nausea, vomiting and constipation; collectively referred to as opioid-induced bowel dysfunction (OIBD). The most prevalent form of OIBD is opioid-induced constipation (OIC) which occurs in up to 87% of patients with pain related to cancer, although rates are approximately 50% in those with non-cancer pain.[106-108] OIC is associated with reduced work productivity and quality of life, yet remains under diagnosed.[109-111] The Rome IV criteria define OIC as a change in bowel habit or defaecatory patterns, in comparison to normal following initiation, alteration or an escalation in opioid therapy,

see Table 1.[20] Two recent cross-sectional studies comparing symptoms and results of diagnostic testing in constipated patients either currently taking or not taking opioids have shown that opioid use is associated with increased symptom severity, diminution in quality of life, and a greater incidence of rectal hyposensitivity, functional ED / dyssynergic defaecation, and delayed whole-gut transit.[112,113]

Mood disorders

The role of psychological factors has been extensively evaluated in the context of functional gastrointestinal disorders (FGIDs). Traumatic events, childhood physical and sexual abuse are independently associated with a higher incidence of FGIDs.[114] The personality trait of neuroticism is particularly associated with constipation.[115] In addition, it is well established that FGIDs are linked with an increased prevalence of concomitant disorders of anxiety and depression although there is controversy as to the directionality of this association. In a large prospective study, Koloski *et al.* demonstrated that higher levels of anxiety, but not depression, conferred an approximate 10% increase in risk of developing a FGID over the subsequent 12 years.[116] In a further study, Jones *et al.* reported that the median time period between diagnosis of an affective disorder and FGID was 3.5 years, compared to a median time period of 1.8 years between a FGID and a diagnosis of an affective disorder.[117] However, this study failed to demonstrate such an association for constipation *per se*.

Areas for future research

1. Further evaluation of the cause and effect relationship between constipation and faecal incontinence.
2. To systematically characterise pathophysiology underlying constipation in hEDS and develop specific evidence-based treatments.
3. Evaluation of the reasons why rates of OIC are higher in cancer pain vs. non cancer pain.
4. Though early-life events may be an important factor in the pathogenesis of paediatric constipation, their impact on chronic (?lifelong) constipation in adults is unknown, and warrants investigation.
5. Prospective evaluation of the potential causal relationship of individual mood disorders on slowing colonic motility and causing constipation.
6. The effect of successful treatment of mood disorders on colonic motility.

PATHOPHYSIOLOGY (see Figure 3)

Colonic dysmotility

Abnormalities of both colonic transit and contractility are commonly associated with CC. Tests of gut transit (see below) can diagnose a patient with normal or slow transit constipation; the latter is typically characterised by delayed movement of intraluminal content through the ascending and transverse colon.[9] In patients found to have delayed transit localised to the distal colon, this may be associated with an ED, though data are conflicting as to whether the transit delay is secondary to the ED or *vice versa*, or indeed they are independent.[9,118] In patients with STC, abnormal colonic contractility has been characterised to an extent, and in comparison to healthy adults, these patients have a reduction in: 1) number of high-amplitude propagating contractions, a propulsive motor pattern associated with mass movement and defaecation;[119-122] 2) the postprandial cyclic propagating motor pattern, which is hypothesized to help mix and control the flow of content (see Figure 4);[123] and 3) pre- and post-prandial colonic pressurizations, synchronous pressure waves recorded across all recording channels, hypothesized to be associated with gas transport.[122] In constipated patients with normal transit constipation or a distal colonic delay, abnormalities of motor activity remain poorly described.

Upper gut dysmotility

Oesophageal, gastric and small bowel motility abnormalities have also been described in patients with CC. A recent study showed that in patients reporting overlapping symptoms of dyspepsia and constipation, those diagnosed with STC were significantly more likely to have a coexistent delay in gastric emptying when compared to those with normal transit constipation.[124] In another study of 91 STC patients, 31 were diagnosed with delayed gastric emptying and 9 had delayed small bowel transit.[125] Manometry studies have additionally shown oesophageal and small bowel contractile dysfunction in constipated patients with normal or delayed colonic transit.[126-128] Whether such findings represent reflex inhibition of proximal GI motility or a shared primary disorder of the enteric nervous system is unknown.

Evacuation disorders

Although the medical literature is littered with synonyms (e.g. defaecation disorder, outlet obstruction, obstructive defaecation disorder, obstructed defaecation etc.), 'evacuation disorder' (ED) is now the accepted term to describe the clinical and / or laboratory features relating to an individual's inability to satisfactorily expel stool.[1,4,9,12] Clinically, the majority of patients with CC complain of

symptoms suggestive of an ED, with straining the most commonly reported individual symptom.[34,130] Indeed 4 of the 6 diagnostic symptoms comprising the Rome IV criteria for FC are compatible with an ED.[20]

The primary pathophysiological mechanisms responsible for EDs are considered to be structural or functional obstructive phenomena that impede the expulsion of stool, though these may overlap.[131] Structural features providing a mechanical barrier to evacuation include high-grade rectal intussusception and enterocoele, whereas misdirected (into 'trapping' rectocoeles, which are usually large, >4 cm)[131] or dissipated force vectors recruited during straining (with descending perineum syndrome and full-thickness rectal prolapse) may also impede evacuatory ability.[4,132] Approximately 7% of patients with symptoms of ED will have a megarectum, allied to diminished or absence of rectal filling sensation.[12,131,132]. Structural phenomena often occur in combination as part of a more global pelvic floor disorder.[131,133,134]

Functional EDs (or FDDs), first described in the mid 1980's,[135-137] are characterised by recto-anal incoordination, manifest as paradoxical involuntary contraction or failure of relaxation of the anal sphincter and pelvic floor musculature (principally puborectalis), and / or inadequate abdomino-rectal propulsive forces.[4,32,132] Functional EDs are often associated with blunted rectal sensation (hyposensitivity),[12,32,138] and also anal hypertonia in a small proportion.[139,140]

On testing, >80% of chronically constipated patients may be diagnosed with pathophysiological features compatible with an ED.[131,141] However, both diagnostic yield and observable cause (structural vs. functional obstruction, or both) are heavily dependent on both the technology used for data acquisition and the approach to data analysis applied.[131,142-144]

Sensory dysfunction

Normal defaecation requires a conscious sensation of rectal filling and urge to defaecate. It is therefore not surprising that impaired or reduced rectal sensation (rectal hyposensitivity: RH; practically defined as a diminished perception to rectal mechanical distension, manifest as elevated sensory thresholds), is associated with disordered defaecation. Observational studies indicate RH is found in up to 60% of constipated patients, 10% of patients with faecal incontinence and 27% of individuals with symptoms of both.[70,145] In the largest study published to date (2,876 patients), 25% of patients were found to have RH, with a linear relationship existing between the number of elevated sensory thresholds to rectal distension and constipation severity.[146]

The aetiology of RH is uncertain, but a number of mechanisms have been proposed. In some patients, in whom there is documented disruption of the afferent pathway (e.g. due to pelvic nerve damage or spinal cord injury),[147,148] there is a clear cause-effect relationship with development of RH. For example, 78% of patients with complete spinal cord injury and hindgut dysfunction, and 43% of individuals with incomplete lesions have RH.[149,150] RH is also an important mechanism in patients with constipation following stroke[151] and associated with multiple sclerosis.[152] In others, behavioural inattention to defaecation (i.e. voluntary withdrawal of attention from rectal sensations and/or habitual suppression of the desire to defaecate) is a likely factor.[153] However, in the majority of patients with chronic constipation, it remains unclear whether RH is a primary pathology leading to increasing severity of symptoms, whether chronic constipation itself results in the development of RH, or if indeed RH is an epiphenomenon.[113,154]

With regard to pathophysiology of RH in CC, this is considered to be either due to dysfunction of the afferent pathway ('primary' RH), as a result of altered rectal wall biomechanics (i.e. increased capacity or hypercompliance ('secondary' RH: see Figure 5), or both.[155] Symptomatically, RH is associated with "no urge constipation"[156,157] and is more common in individuals meeting the Rome IV criteria for FC (60%) rather than IBS-C (2%).[145] RH appears to be linked primarily to ED,[138] and particularly with "functional" rather than a mechanical (anatomical) obstruction to defaecation.[12,32,70,138,158]

RH impacts CC via two key mechanisms: 1) through its association with functional ED either directly, due to co-incident/corresponding efferent dysfunction (i.e. concurrent reduced rectal contractility),[154,159] or indirectly via the development of large, hard and difficult to evacuate stools due to faecal retention and desiccation secondary to reduced awareness; and 2) due to colonic transit delay via inhibitory feedback loops triggered by chronic rectal distension.[160,161]

Genetic factors and enteric neuropathies

The question of whether CC (especially STC) occurs as a result of an enteric neuropathy, and whether this might be genetically determined has prevailed in the scientific literature since the 1960s, being mainly predicated on clinical observations of early-onset symptomatology and positive family history.[162-164] However scrutiny of this literature shows little or no evidence of Mendelian inheritance, unaffected monozygotic twins, and where studied, similar rates of family history in community controls.[162] The hypothesis is also attractive because of the known genetic causation of certain bona fide enteric neuropathies, notably Hirschsprung disease. The finding of kindreds (some with a

Mendelian disposition) where Hirschsprung and STC co-segregate[164,165] has prompted candidate gene approaches such as for mutations of the *RET* gene in patients with STC. These have proved unrewarding.[166] It seems likely that a search for a genetic aetiology will be consigned to genome-wide association studies, which have determined weak susceptibility factors in IBS-C,[167] or to recognition that epigenetic factors may be more important.

The question of whether an enteric neuropathy underpins the transit disturbance in STC is mired by issues of defining neuropathy histologically. This issue is part technical (right specimen, adequate sampling, right preparation, right staining etc.) and part interpretive, the latter being especially problematic when neuronal quantification is attempted.[168] Thus early reports using sledge microtome thick sections and silver staining[169,170] should be discounted in favour of modern approaches.[171] With the exception of a single high quality study from Germany,[172] it is fair to summarise that there is no strong evidence for neuropathy based either on cytoskeletal evidence of cell degeneration or of quantifiable neuronal loss (based on 12 studies from the modern era).[171]

Dysbiosis

Numerous case-control studies have now compared the gastrointestinal microbiome between CC, IBS-C and healthy controls. In general, studies in adults report lower bifidobacteria and bacteroides in constipation, with some also reporting lower lactobacilli, although these findings are not consistently demonstrated in paediatric patients.[173]

One noteworthy study using 16S ribosomal RNA gene sequencing to measure both stool and mucosal microbiome reported marked differences in mucosal microbiome at both the family level (lower proportions of Comamonadaceae and Odoribacteraceae, higher Flavobacteriaceae and Caulobacteraceae) and genus level (higher Flavobacterium and Mycoplana, lower Delftia and Odoribacter).[174] Multivariate analysis (adjusting for age, body mass index, diet) showed that although stool microbiome composition was significantly associated with colonic transit time, it was mucosal microbiome composition that was significantly associated with constipation even after adjusting for transit time.[174]

In terms of microbiome metabolites, there is inconsistent evidence regarding differences in short-chain fatty acids (SCFA) between constipated and healthy subjects; one challenge being that slower colonic transit time can reduce stool SCFA by increasing their colonic absorption rather than decreasing their production.[175] Meanwhile, positive methane breath tests to a carbohydrate challenge

have been shown in some (but not all)[176] studies to be more common in people with STC than both normal transit constipation and healthy controls,[176,178] and also in IBS-C compared to diarrhoea-predominant IBS.[179] Nevertheless, there appears to be no correlation between methane production and constipation symptom severity.[180] Furthermore, observational case-control studies that have identified alterations in the microbiome and their metabolites are unable to establish whether these differences are a cause or merely as a consequence of constipation.

A direct causal relationship of the microbiome on gut motility has been demonstrated in mice, where the prolonged whole gut transit time in germ-free mice (457 min) was shown to be shortened in germ-free mice colonized with human microbiome (285 min), and this was related to greater colonic contractility in the humanised mice.[181] Furthermore, manipulation of murine whole gut transit time led to profound changes in gut microbiome. Polyethylene glycol induced more rapid transit time and resulted in lower abundance of Peptococcaceae, Eubacteriaceae, and Anaeroplasmataceae and higher Bacteroidaceae and Peptostreptococcaceae, whilst loperamide induced slower transit time and resulted in a higher Firmicutes:Bacteroidetes ratio and lower Lachnospiraceae.[181] These murine experiments identify a role for the gut microbiome in influencing gut transit and imply that the altered microbiome described in human case-control studies may, in part at least, be a factor involved in the pathogenesis of constipation.

Areas for future research

1. While motor and transit abnormalities have been recorded through various regions of the gut in patients with constipation, we still have a poor understanding of i) how motor patterns relate to movement of content; and ii) how motor patterns in one region of the gut relate to motor patterns in adjacent regions. Are abnormal motor pattern in the small bowel part of a general pan-enteric disorder or secondary to reflex inhibition as a consequence of delayed transit through the colon?
2. There is recognised overlap between ED and delayed whole gut / colonic transit. The question as to which is primary and which is secondary (or do they coexist?) remains an area of debate and warrants further research.
3. While the presence of RH can negatively impact on treatment outcomes,[182] RH itself has been proposed as a therapeutic target.[183] Specific sensory bowel retraining therapy has been shown to improve sensory dysfunction (in up to 92% of individuals) with corresponding improvement in symptoms.[184,185] However, further high quality controlled studies are required and this is an orphan area for drug development.

4. Further studies are also required to define the overall clinical impact of RH in hindgut dysfunction.
5. An understanding of dysbiosis and its effects on nerves either directly or via longer term epigenetic changes in nerves or glia are needed. Fundamental studies are required to understand how enteric neurons survive, if they turnover and whether they do so from glia or neuronal progenitors.

FUNCTIONAL DIAGNOSTIC INVESTIGATIONS

Advanced diagnostic studies of colonic, rectal and anal function are recommended in patients in whom organic disease has been excluded, who have failed first-line conservative therapies, such as optimisation of stool consistency, bowel habit training and lifestyle advice, and who are also refractory to standard pharmacological treatments.[186,187] The aim of investigation is to provide clinically relevant measurements that explain the cause of symptoms, identify pathology, and guide effective management. No one technique provides a complete description of defaecation; instead, a combination of tests to evaluate structure, motor and sensory function are generally employed.[129] Unfortunately, inconsistency in approach exists due to conflicting data on the usefulness of these investigations for decision making, variability in local expertise and resource availability. Below is a description of the use, merits and pitfalls of the most commonly employed techniques (see also Table 2).

Tests of gut transit

In patients with CC, tests of transit may be useful in those who report infrequent defaecation. Although traditional radiological methods (radio-opaque markers [ROM] and scintigraphy) tend to focus on quantification of colonic transit, it is now appreciated that dysmotility is not necessarily restricted to the colon (see above) and therefore newer techniques (wireless motility capsule [WMC] and 3D-Transit method) have the ability to assess pan-enteric function.

ROM testing is considered a screening investigation, and is indicated to differentiate between normal and slow whole-gut transit (often reported as 'colonic' transit time, though this is overestimated, as oro-caecal transit is a mean of 8 hours, even in healthy volunteers).[188] The test is inexpensive and easy to perform, and results correlate with stool form; for example, prolonged transit time is associated with hard stools. Several ROM protocols exist; the simplest involves the intake of markers (typically 20 – 50) at a single time-point, followed by a single abdominal X-ray, usually after 120 h;[189] transit is defined as abnormal if >20% of markers are retained at the time of the X-ray (see Figure 6A).[189] This

provides a surrogate of disease severity that is more accurate than subjective assessment of faecal loading on an X-ray film.[190] Alternatively, markers can be taken on consecutive days, enabling assessment of mathematically-derived whole-gut and regional colonic transit times.[191,192] However, such calculations are based on the assumption that transit time is a continuous variable; recent studies employing other methods (e.g. WMC and 3D-Transit) have demonstrated, in sizeable healthy volunteer studies, that whole-gut transit times are, in fact, clustered at intervals separated by approximately 24 hours.[188,193]

Scintigraphy is recognised as the 'gold-standard' method for assessing colonic transit time, but availability is limited to a few specialist centres.[194] The technique involves following the progress of a radioisotopic chemical (e.g. ^{111}Indium) through the GI tract using a gamma camera and taking serial scintigrams.[195] Diagnosis of delayed colonic transit is determined by position of the geometric centre of the isotope mass at given time points. The test can be extended to include assessment of gastric and small bowel transit also.[196]

The WMC (SmartPill, Medtronic, USA) and 3D-Transit system (Motilis Media, SA, Lausanne, Switzerland) are ingestible capsule devices. The WMC is commercially available, and measures pH, temperature and intraluminal pressure as it traverses the gut.[192,197] Total and regional gastrointestinal transit times are determined from stereotypical changes in pH and temperature (see Figure 6B); however, accurate information on segmental colonic transit times cannot be determined. The test has been validated against ROM and scintigraphy.[197,198] At present, the 3D-Transit system is an experimental investigation only; through tracking of the location and orientation of ingested electromagnetic capsules, it offers the potential to assess total and regional GI transit times, segmental colonic transit times,[193] and also colorectal motility patterns.[199]

Tests of colonic motility

Colonic manometry can be employed for advanced investigation of colonic motility in highly selected patients.[187] It is generally used to determine the presence or absence of colonic motor patterns in response to physiological and chemical stimuli.[200] Several protocols exist, but most commonly, after bowel preparation, a catheter incorporating >20 recording sensors, spaced between 10 – 30 mm apart, is placed into the colon with the aid of a colonoscope.[201] With the subject awake, data is collated over a 1-2 hour period before and after a high calorie meal. This can then be followed by assessing the colonic response to intraluminal infusion of a stimulant laxative (e.g. Bisacodyl).[202] Though information on colonic motility patterns and propagating sequences can be acquired, standardisation of the

technique is in its infancy.[202] Catheter types, the number of sensors and the spacing between them, types of meals and the analysis and interpretation of results all differ amongst different centres. Further, due to a limited number of studies in healthy subjects, a clear definition of 'normal' colonic motility is lacking. Nevertheless, high-resolution techniques are revealing motor patterns that were previously undetected using conventional technology.[203]

The use of magnetic resonance imaging (MRI) to investigate colonic motility is experimental at present, but allows for the direct visualisation of either colon wall[204] or the contents of the lumen.[205] Using cine MRI and post-processing techniques,[206] it is possible to track colon wall motion prior to and following a laxative challenge[207] and to visualise how the luminal contents are moving, using spatio-temporal maps of luminal contraction and dilation. Further, assessment of colonic wall motion can be combined with other MRI measures e.g. transit[208] and volume,[209] to provide an objective view of the colon, both in terms of anatomy and function.

Tests of evacuation

Tests of evacuation are useful in patients with CC, especially those who report symptoms of ED. The balloon expulsion test (BET) and defaecography are direct measures of the ability to expel rectal contents, whereas high-resolution anorectal manometry (HR-ARM) is an indirect test of evacuation, which, in this setting, provides information primarily on recto-anal co-ordination.

The BET is a widely used, simple, inexpensive, office-based test that is easy to interpret. It is used as a screening investigation of evacuation, and provides quantitative information on the time taken to expel a 50 ml water-filled rectal balloon. The upper limit of normality is generally accepted to be between 1-3 minutes, and expulsion times that exceed this suggest impaired evacuation.[210,211] Though there is good test reproducibility, and results help predict response to biofeedback therapies,[212] BET provides information only on the ability and time taken to evacuate, not on the reason for failure (e.g. obstructive anatomy or dyssynergia).[129] Further, the use of a small balloon is criticised as a poor analogue for stool which may not generate a normal urge to defaecate.[211]

Defaecography is the only direct test of evacuation which provides detail of anatomical variants which may obstruct rectal emptying, as well as identifying 'functional' obstructive causes.[131] It may be performed using fluoroscopy or MRI,[131] with a contrast paste inserted into the rectum to act as a stool surrogate. The patient is then asked to evacuate this paste while representative images are acquired. Physical barriers to expulsion (e.g. rectocele, enterocoele, intussusception) can be described, as well

as ability to co-ordinate the pelvic floor musculature during evacuatory manoeuvres.[131,213] MRI in particular provides excellent assessment of all pelvic floor compartments.[214] Defaecography, when performed in the sitting position with a native urge to defaecate, is considered the test of evacuation with the most construct validity.[129] Nevertheless, there is significant variability in measures used for reporting of results which limits transferability of data.[131] Additionally there is some overlap of findings between symptomatic and control subjects, especially in parous women.[215] MRI defaecography is criticised for generally being performed in the supine position, as open-magnet scanners, that allow imaging in the upright position, are available only in specialised centers.[216] Barium defaecography does not image soft tissues and requires the use of ionising radiation. Pelvic floor ultrasound may be considered an alternative indirect screening test, in that it allows visualisation of prolapse of pelvic floor structures, though the consequences of any identified prolapse on evacuatory function are unclear from this investigation alone.[217,218]

HR-ARM is widely available and easy to perform. As part of a standardised protocol recommended by the International Anorectal Physiology Working Group,[219] the 'push' manoeuvre provides information on recto-anal co-ordination through simultaneous measurement of both anal and rectal pressures. Data are interpreted both quantitatively and qualitatively, with the aid of colour contour plots.[219] Together with an abnormal direct test of evacuation (BET of defaecography), abnormal patterns of recto-anal co-ordination, manifest as poor rectal propulsion and/or anal dyssynergia, are used to diagnose dyssynergic defaecation,[32] recognised in the new international 'London' Classification as minor disorders of anorectal function.[219] HR-ARM is recommended to be performed in the left lateral position with an empty rectum[129], but has poor content validity under such circumstance; studies in the upright, seated position are feasible and evidence is accumulating to suggest that this may improve test performance.[220-222] However, interpretation can be difficult as there is a wide overlap of findings between symptomatic and control subjects. In particular, blinded diagnostic accuracy studies suggest that specificity of previously well accepted manometric patterns of dyssynergia may be as low as 13%.[223] This contrasts with a high level of diagnostic agreement between qualitative assessment of HR-ARM data and MRI defaecography for dyssynergic defaecation,[224] highlighting the requirement for results of indirect and direct tests of evacuation to be consistent.

One emerging tool is Fecobionics,[225] a 10 cm long simulated stool probe containing various sensors assessing pressure, orientation, and bending during evacuation. It combines a direct assessment of evacuation time (validated against BET) with physiological measurements detailing recto-anal

coordination and rectal sensation. Novel evacuation patterns are also described using preload-afterload pressure analysis.[225]

Tests of rectal sensation

Tests of rectal sensation are an essential part of the comprehensive diagnostic assessment of individuals with CC, as intact visceral sensory pathways are essential to normal bowel function. Distension of the rectum using an intrarectal balloon[226] is the most widely employed method for quantifying rectal sensitivity, and is often performed as part of an anorectal manometry protocol. The London Classification[219] recommends documentation of three sensory thresholds using a ramp distension or incremental phasic distension protocol: first constant sensation volume, defaecatory desire volume and the maximum tolerated volume. Elevated thresholds indicate rectal hyposensitivity, diminished thresholds indicate rectal hypersensitivity.[219] Balloon distension is economical, technically easy and accessible. However, it is confounded not only by inflation protocols[227] but also the elastic recoil properties of the balloon itself, and thus, in the presence of abnormal sensory thresholds, the test cannot distinguish between afferent nerve dysfunction, hyper/hypo-compliance or dilation of the rectum.[228] Accordingly, balloon distension should be considered a screening test of visceral sensation.

The recognised gold-standard for determining visceral sensation to distension is the electromechanical barostat,[226,229] a computer-controlled piston connected to a distensible bag with a volume larger than the viscus being examined (i.e. the bag is effectively infinitely compliant). The bag is inflated and deflated automatically to maintain a constant pressure within the rectum while volume is continuously recorded.[230] Barostat recordings are not affected by the recoil properties of the bag, hence permitting the determination of rectal wall bio-elastic properties (e.g. compliance and capacity: see Figure 5).[226,228,231,232] The test is reproducible across laboratories and between patients.[229,233] However, restricted availability, expense and procedure duration have limited barostat use in clinical practice. To address these issues, recent efforts have been made to validate short barostat protocols[234,235] and to develop simple bedside tests, such as the use of a portable device (Rapid Barostat Bag Pump, Mui Scientific, Canada).[235]

Areas for future research

1. Prospective, controlled studies are still required to establish the role of routine diagnostic investigations (e.g. transit study, tests of evacuation, and rectal sensitivity testing) and other measurement tools in stratifying treatment.

2. To further develop comprehensive testing to assess the relative importance of colonic motility, rectal motor-sensory function and patient behaviour at the level of the individual patient.
3. Large, preferably multicentre studies in healthy adults are needed to established normal ranges of colonic motility patterns in response to standardised stimuli (meals, sleep, chemical stimulation).
4. MRI 'motility' techniques need to be further developed to cover all segments of the colon, thus avoiding the need for more invasive tests.
5. Given the acknowledged major overlap between health and CC,[223] and poor agreement between results of different tests,[144,224] the optimum method(s) for the diagnosis of dyssynergic defaecation requires re-evaluation.
6. Assessment of the impact of the London Classification for disorders of anorectal function; it is hoped that the use of a common language to describe results of diagnostic tests, standard operating procedures, and a consensus classification system will bring much-needed standardisation. This is projected to facilitate co-operation between centres and the performance of multi-centre studies, a key requirement if progress is to be made towards improved diagnosis and individually tailored therapy of patients with these conditions.

SUMMARY & CONCLUSIONS

Chronic constipation is common, problematic for the sufferer and complex for the physician. This review has sought to coalesce up-to-date information on several key aspects of CC. The content should provide an educational resource for the reader with a clinical or research interest in this disease area. It also frames the background for the sister review addressing therapy. It is hoped that some of the many areas of future research outlined will be addressed by a future generation of readers.

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FIGURE LEGENDS

Figure 1. Schematic drawing demonstrating the symptom-based spectrum of functional constipation (FC) and irritable bowel syndrome with constipation (IBS-C), and biomarkers that may be used to discriminate these conditions from each other. From Whitehead et al 2016.[43] (With permission from Wiley)

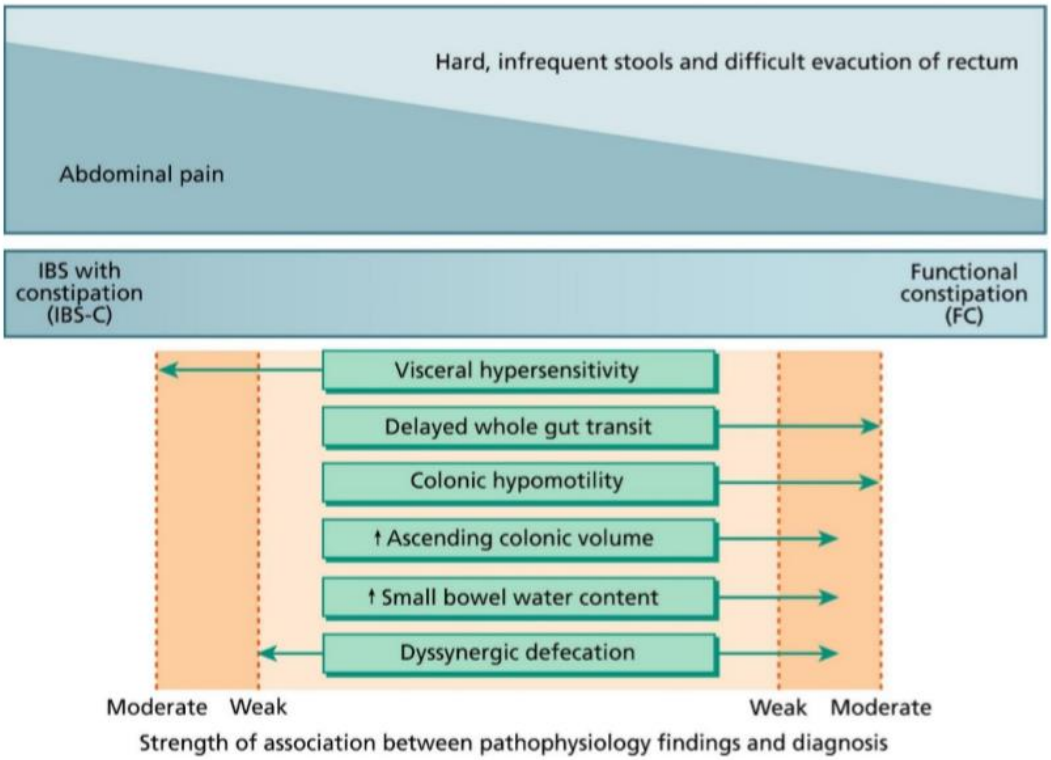


Figure 2. Schematic drawing highlighting the multifactorial pathophysiological mechanisms common to coexistent faecal incontinence (FI) and chronic constipation (CC).[65,67,70,73]

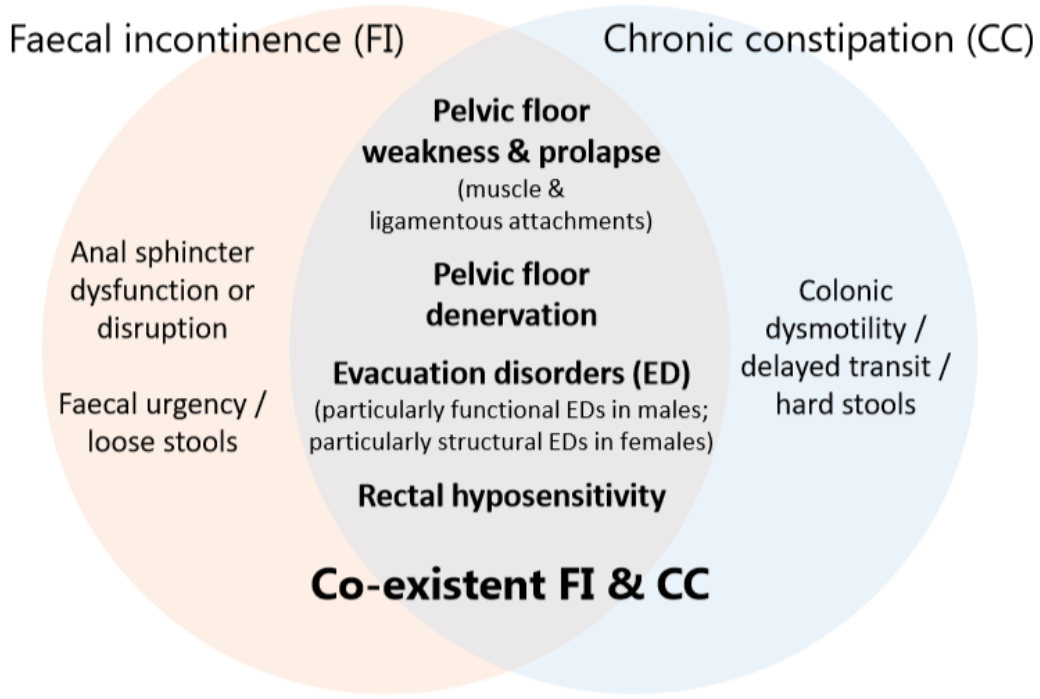


Figure 3. Schematic of principal (overlapping) pathophysiological mechanisms in chronic constipation.

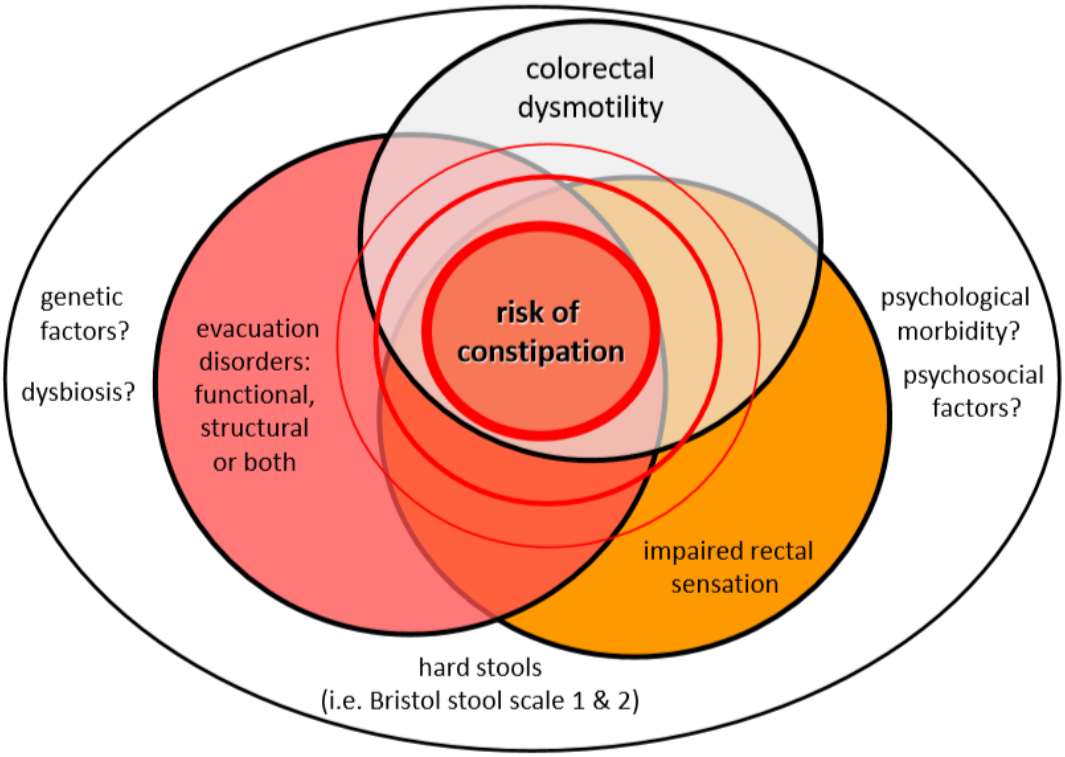


Figure 4. Representative example of a meal response in the descending and sigmoid colon of a healthy adult (A) and a patient with STC (B). In the top two images (A and B), the entire recording is shown 2 h prior to and after the meal. A rapid increase in colonic activity can be seen in the healthy subject after the meal is given (Blue line); this response is not evident in the patient. In (C) and (D), an expanded section of the meal response is shown from the area inside the red-hatched boxes in the top two images. In (C), the retrograde cyclic motor pattern is evident (purple arrow). In the expanded section of the patient trace (D) 2–3 cpm activity can be seen, but the cyclic propagating motor pattern is not evident. In this section of the trace, two retrograde short single motor pattern can be seen (purple arrows). The spatiotemporal pressure plots of (C) and (D) are shown in (E) and (F). The purple arrows in (C) and (D) are shown as white arrows in the bottom two images. From Dinning et al, 2015.[123]
(With permission from Wiley)

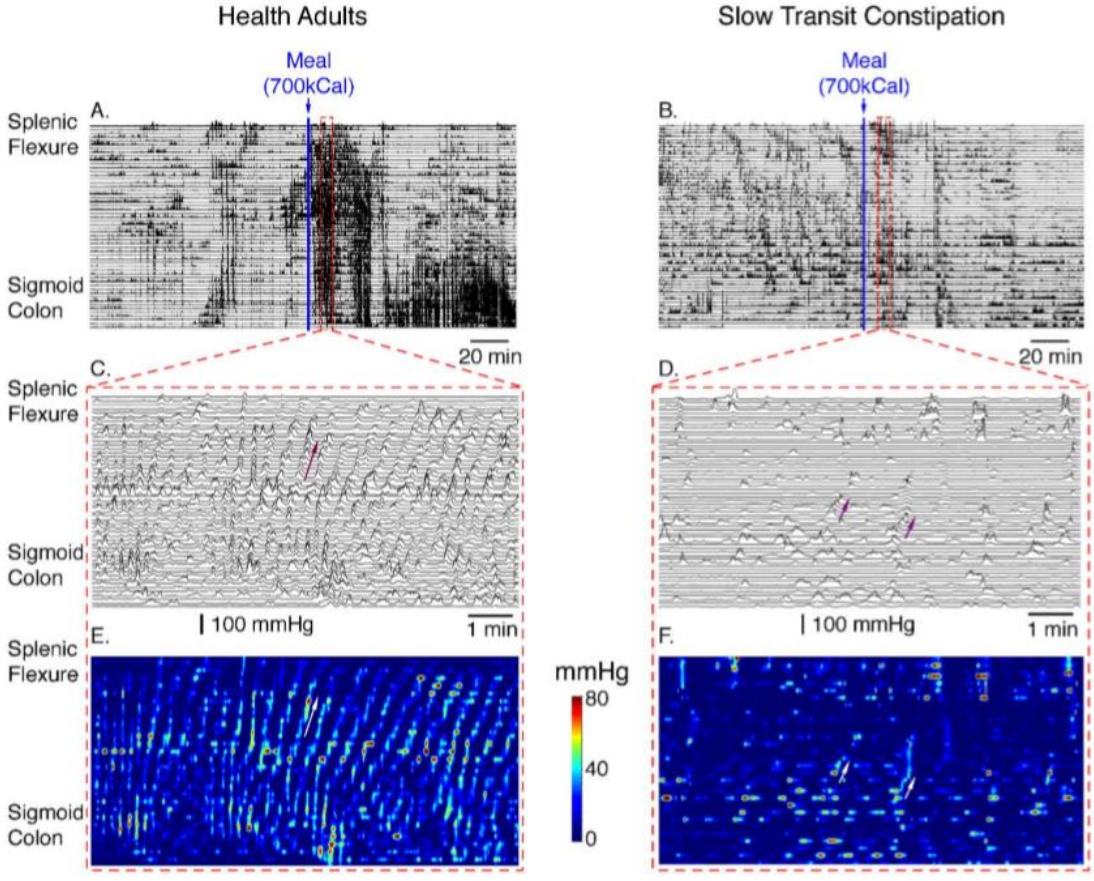


Figure 5. Rectal pressure-volume relationships determined through use of the electromechanical barostat (phasic isobaric distension protocol) in constipated patients with rectal hyposensitivity (RH) to balloon distension, constipated patients with normal rectal sensation (NS), and healthy volunteers (HV). Both rectal capacity (reflected by elevated distension volumes) and rectal compliance (steeper slope of the linear section of the curve) are increased in patients with RH. Adapted from Gladman et al.[228]

(With permission from Wolters Kluwer)

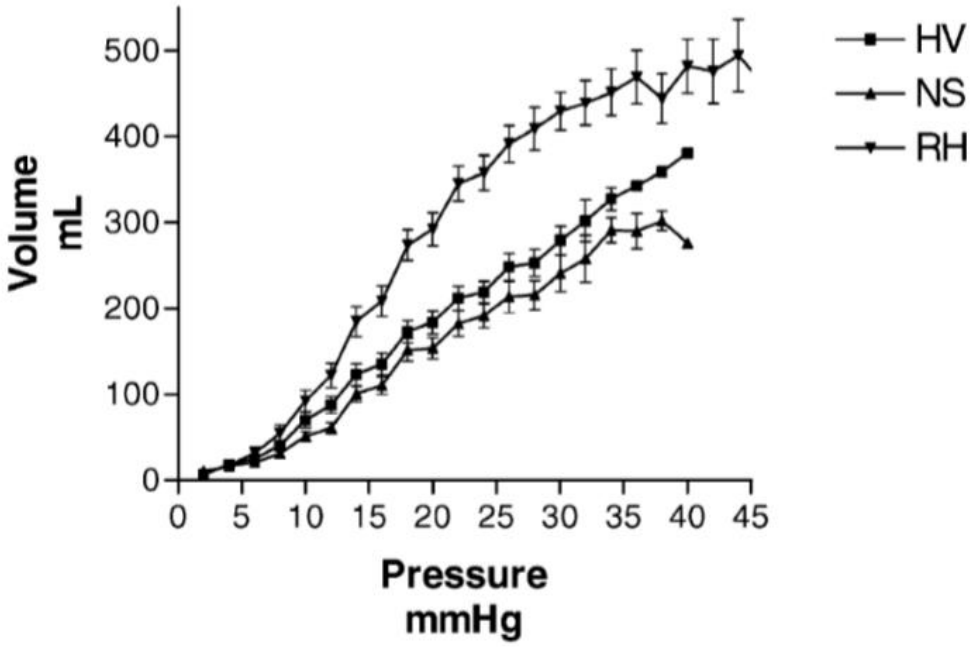
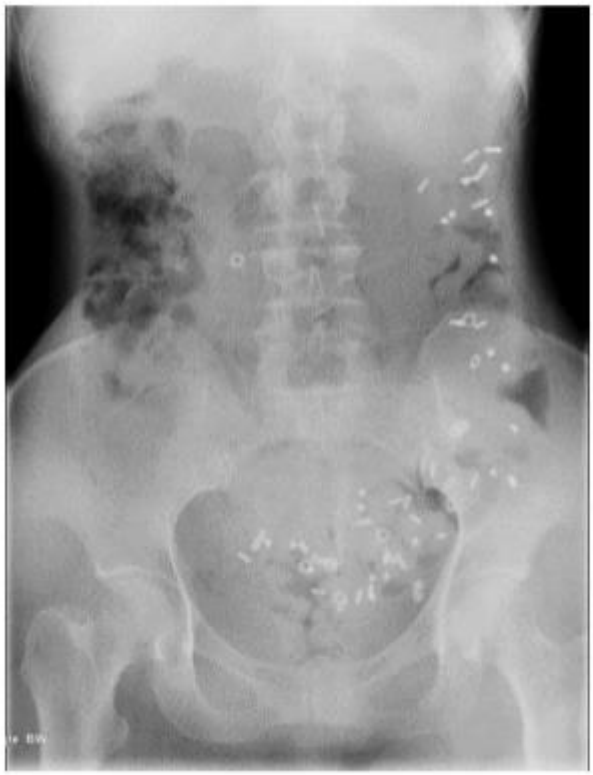
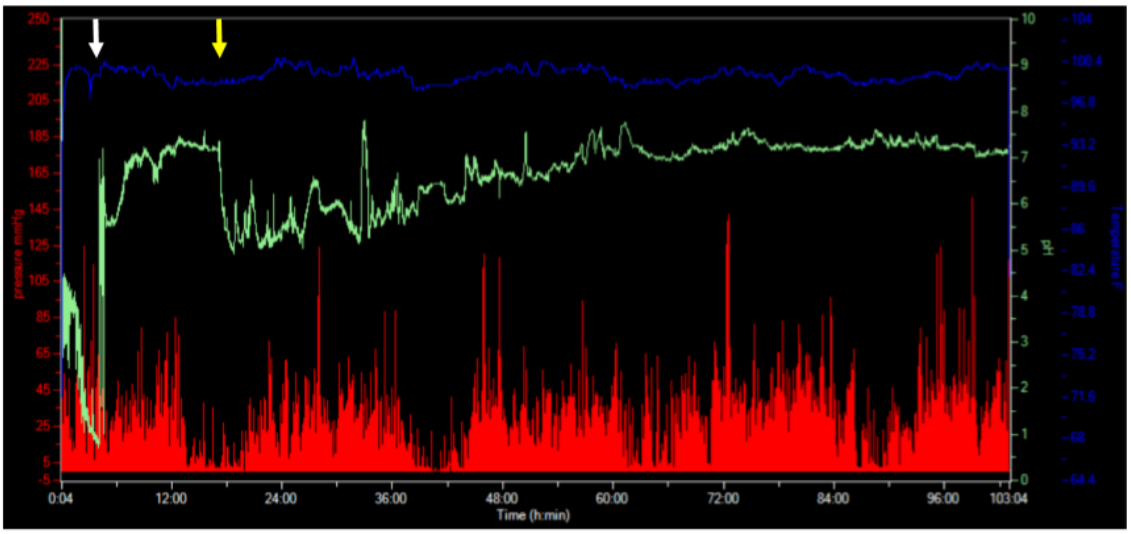


Figure 6. Examples of both a screening method (A: plain abdominal X-ray following previous ingestion of radio-opaque markers) and more advanced method (B: full Wireless Motility Capsule study) for the diagnostic assessment of whole-gut transit. The X-ray shows retention of all 60 ingested markers (Metcalf method:[191] 3 different marker sets) at 120 hr, clearly demonstrating a pathological delay in whole-gut transit (≥20% of markers remaining). The Wireless Motility Capsule study (different patient) shows temperature (blue trace), pH (green trace) and pressure (red trace) changes throughout the study period. Using stereotypical alterations in the pH profile (abrupt rise [white arrow] – stomach to small bowel transition, and sharp drop [yellow arrow] – small to large bowel transition), regional GI transit can be determined. This recording shows normal gastric emptying (3 hr 55 min; upper limit of normal: 5 hr[188]), but a pathological delay in transit through both the small bowel (13 hr 3 min; upper limit of normal: 8 hr[188]) and colon (85 hr 45 min; upper limit of normal: 50 hr 30 min[188]). Whole-gut transit time (from ingestion, left border of recording to expulsion, left border of recording) is also delayed (102 hr 44 min; upper limit of normal: 68 hr 45 min[188]).

A



B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pH
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86
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75.2
71.6
68
64.4
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48:00
60:00
72:00
84:00
96:00
103:04
Time (h:min)

Table 1 – The Rome IV diagnostic criteria for opioid-induced constipation.

The Rome IV Diagnostic Criteria for Opioid-Induced Constipation
1. New, or escalating, symptoms of constipation when initiating, changing or increasing opioid therapy that must include 2 or more of the following: A) Straining during more than one quarter of defaecations B) Lumpy or hard stools (BSFS 1-2) more than one-quarter of the time C) Sensation of incomplete evacuation more than one-quarter of the time D) Sensation of anorectal blockage/obstruction in more than one-quarter of defaecations E) Manual manoeuvres to facilitate more than one-quarter of defaecations F) Fewer than three spontaneous bowel movements per week 2. Loose stools rarely present without the use of laxatives

Table 2 – Diagnostic investigations for chronic constipation.

Investigation	*Screening, advanced or experimental*	*Resources required**	*Principal pathophysiological information provided*	*Other pathophysiological information provided*
Tests of gut transit				
Radio-opaque markers	Screening	+	Delayed whole gut transit	
Scintigraphy	Advanced	+++	Delayed colonic transit	Delayed regional GI and whole gut transit (extension of technique)
Wireless Motility Capsule	Advanced	++	Delayed regional GI and whole gut transit	Regional GI dysmotility; dysbiosis / altered colonic fermentation?
3D-Transit capsule	Experimental	++	Delayed regional GI and whole gut transit	Regional GI dysmotility
Tests of gut contractility				
Colonic manometry	Advanced	+++	Colonic dysmotility	
Colonic barostat	Advanced	++	Altered colonic tone	Colonic dysmotility
Real-time MRI	Experimental	+++	Colonic dysmotility (altered wall motion)	Alterations in colonic luminal volume
Tests of evacuation				
Anorectal manometry	Screening	++	Abnormal recto-anal co-ordination; poor rectal propulsion; anal dyssynergia	Anal sphincter dysfunction
Balloon expulsion test	Screening	+	Impaired evacuation	
Transperineal ultrasound	Screening	++	Functional and / or structural obstructive features	
Barium defaecography	Advanced	+++	Impaired evacuation; functional and / or structural obstructive features	Multi-compartmental abnormalities (when appropriately opacified)
MRI defaecography	Advanced	+++	Impaired evacuation; functional and / or structural obstructive features	Multi-compartmental pelvic floor abnormalities
Fecobionics	Experimental	++	Impaired evacuation	Abnormal evacuation pressure patterns
Tests of sensation				
Balloon distension	Screening	+	Rectal hypo- and hypersensitivity	
Barostat	Advanced	++	Rectal hypo- and hypersensitivity	Abnormal rectal compliance and capacity

MRI = magnetic resonance imaging

** relates to cost and availability (+ = cost-effective and / or widely available; +++ = expensive and / or of limited availability)*